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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILSON, LARRY ROSS	

ART UNIT	PAPER NUMBER
3767	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/803,711	KEIMEL ET AL.	
	Examiner	Art Unit	
	LARRY R. WILSON	3767	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,10,12,14,16-21,23-26,28-34,44-49,51,52,54-60,62,63,65,66,68-75 and 129-140* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-7,9,10,12,14,16-21,23-26,28-34,44-49,51,52,54-60,65,66,68-75 and 129-140.

DETAILED ACTION

Claim Objections

1. Applicant is advised that should claim 1 be found allowable, claim 54 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-6, 9, 10, 12, 14, 18-21, 23-26, 28-33, 45-49, 51-52, 54-59, 62, 63, 65, 66, 69-75, and 129-140 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,814,014 to Dennis D. Elsberry et al. (Elsberry) in view of U.S. Patent 5,433,946 to Howard J. Allen, Jr. et al. (Allen), U.S. Patent Application 2003/0129186 to Richard Beliveau et al (Beliveau), U.S. Patent 5,911,969 to Donald B. Axworthy et al. (Axworthy) and non-patent literature entitled "Crystallographic analysis of the pH-dependent binding of iminobiotin by streptavidin" to Francis K. Athappilly et al. (Athappilly).

In regards to claim 1, Elsberry teaches a system comprising an implantable catheter system (Fig. 1, #22), and a pump (Fig. 1, #10) that pumps said therapeutic protein formulation through said implantable catheter system to at least one targeted

region (col. 3, lines 19-20), wherein the pump provides for a programmable delivery rate of the therapeutic protein formulation (col. 4, lines 32-36), and wherein the delivery rate is selected based on factors selected from the group consisting of specific neurological disease (col. 3, line 66-col. 4, line 3 – shows the sensing of hyperexcitation indicative of neurological disease), genetic sequence of the patient's gene encoding for the protein to be delivered, body weight, and combinations thereof.

But Elsberry does not teach a therapeutic protein formulation that has been modified for enhanced cellular uptake properties, wherein at least some of the proteins within said therapeutic protein formulation have been modified to comprise a transport aid, said modified proteins have been modified by conjugation to a transport aid that facilitates the cellular uptake of said therapeutic protein

Allen teaches a therapeutic protein formulation that has been modified for enhanced cellular uptake properties (col. 3, lines 45-51, col. 4, line 46-47), wherein at least some of the proteins within said therapeutic protein formulation have been modified to comprise a transport aid (Allen col. 4, lines 44-47), said modified proteins have been modified by conjugation to a transport aid that facilitates the cellular uptake of said therapeutic protein (col. 4, lines 44-47).

Neither Elsberry nor Allen teaches the conjugation comprises a linker species existing between said therapeutic protein and said transport aid; said linker is a streptavidin-biotin complex.

Beliveau teaches the conjugation comprises a linker species existing between said therapeutic protein and said transport aid (para. 26); said linker is a streptavidin-biotin complex (para. 189).

Neither Elsberry, Allen or Beliveau teaches linking the protein with the transport aid in a pH-dependent manner wherein the therapeutic protein and transport aid remain operably linked in a neutral pH environment, and the therapeutic protein disassociates at an acidic pH.

Axworthy teaches linking the protein with the transport aid in a pH-dependent manner (col. 19, lines 29-40).

But Elsberry, Allen, Beliveau, or Axworthy teaches that the therapeutic protein and transport aid remain operably linked in a neutral pH environment, and the therapeutic protein disassociates at an acidic pH.

Athappilly teaches the therapeutic protein and transport aid remain operably linked in a neutral pH environment, and the therapeutic protein disassociates at an acidic pH (abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have included the therapeutic protein formulation of Allen, and the linker species of Beliveau in the system of Elsberry, in order to in order to reduce therapeutic protein loss to clearance and inactivation (col. 1, lines 48-51, 62-64) as taught by Allen, and to modulate blood-brain barrier transport (abstract) as taught by Beliveau.

Furthermore, one of ordinary skill would have found it obvious to include a pH dependent linkage of Axworthy and the low pH dissociation of Athappilly in the system

of Elsberry, Allen, and Beliveau, in order to provide clearing agents to facilitate removal of circulating targeting complexes (col. 1, lines 58-64) as taught by Axworthy.

In regards to claim 28, Elsberry teaches a system comprising a means of physically bypassing the blood-brain barrier, via an implantable catheter system (Fig. 1, #22), and a pump (Fig. 1, #10) that pumps said therapeutic protein formulation through said implantable catheter system to at least one targeted region (col. 3, lines 19-20), wherein the pump provides for a programmable delivery rate of the therapeutic protein formulation (col. 4, lines 32-36) and wherein the delivery rate is selected based on factors selected from the group consisting of specific neurological disease (col. 3, line 66-col. 4, line 3 – shows the sensing of hyperexcitation indicative of neurological disease), genetic sequence of the patient's gene encoding for the protein to be delivered, body weight, and combinations thereof.

But Elsberry does not teach a means for providing a therapeutic protein formulation that has been modified for enhanced cellular uptake properties, wherein at least some of the proteins within said therapeutic protein formulation have been modified to comprise a transport aid that provides for enhanced cellular uptake of said modified proteins, said modified proteins have been modified by conjugation to a transport aid that facilitates the cellular uptake of said therapeutic protein.

Allen teaches a therapeutic protein formulation that has been modified for enhanced cellular uptake properties (col. 3, lines 45-51, col. 4, line 46-47), wherein at least some of the proteins within said therapeutic protein formulation have been modified to comprise a

transport aid that provides for enhanced cellular uptake of said modified proteins (Allen col. 4, lines 44-47), said modified proteins have been modified by conjugation to a transport aid that facilitates the cellular uptake of said therapeutic protein (col. 4, lines 44-47).

Neither Elsberry nor Allen teaches the conjugation comprises the conjugation comprises a linker species existing between said therapeutic protein and said transport aid; said linker is a streptavidin-biotin complex.

Beliveau teaches the conjugation comprises a linker species existing between said therapeutic protein and said transport aid (para. 26); said linker is a streptavidin-biotin complex (para. 189).

Neither Elsberry, Allen or Beliveau teaches linking the protein with the transport aid in a pH-dependent manner wherein the therapeutic protein and transport aid remain operably linked in a neutral pH environment, and the therapeutic protein disassociates at an acidic pH.

Axworthy teaches linking the protein with the transport aid in a pH-dependent manner (col. 19, lines 29-40).

But Elsberry, Allen, Beliveau, or Axworthy teaches that the therapeutic protein and transport aid remain operably linked in a neutral pH environment, and the therapeutic protein disassociates at an acidic pH.

Athappilly teaches the therapeutic protein and transport aid remain operably linked in a neutral pH environment, and the therapeutic protein disassociates at an acidic pH (abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have included the therapeutic protein formulation of Allen, and the linker species of Beliveau in the system of Elsberry, in order to in order to reduce therapeutic protein loss to clearance and inactivation (col. 1, lines 48-51, 62-64) as taught by Allen, and to modulate blood-brain barrier transport (abstract) as taught by Beliveau.

Furthermore, one of ordinary skill would have found it obvious to include a pH dependent linkage of Axworthy and the low pH dissociation of Athappilly in the system of Elsberry, Allen, and Beliveau, in order to provide clearing agents to facilitate removal of circulating targeting complexes (col. 1, lines 58-64) as taught by Axworthy.

In regards to claim 54, Elsberry teaches a system comprising an implantable catheter system (Fig. 1, #22) to physically deliver said therapeutic protein formulation across the blood-brain barrier at a programmed delivery rate (col. 4, lines 32-36) for the purpose of treating patients diagnosed with at least one neurological disease of the central nervous system (abstract), a pump (Fig. 1, #10) that pumps said therapeutic protein formulation through said implantable catheter system to at least one targeted region (col. 3, lines 19-20), wherein the pump provides for a programmable delivery rate of the therapeutic protein formulation (col. 4, lines 32-36), and wherein the delivery rate is selected based on factors selected from the group consisting of specific neurological disease (col. 3, line 66-col. 4, line 3 – shows the sensing of hyperexcitation indicative of neurological disease), genetic sequence of the patient's gene encoding for the protein to be delivered, body weight, and combinations thereof.

But Elsberry does not teach a therapeutic protein formulation, wherein at least some proteins within said therapeutic protein formulation have been modified to comprise a transport aid that provides for enhanced cellular uptake of said modified proteins, said modified proteins have been modified by conjugation to a transport aid that facilitates the cellular uptake of said therapeutic protein.

Allen teaches a therapeutic protein formulation that has been modified for enhanced cellular uptake properties (col. 3, lines 45-51, col. 4, line 46-47), wherein at least some of the proteins within said therapeutic protein formulation have been modified to comprise a transport aid that provides for enhanced cellular uptake of said modified proteins (Allen col. 4, lines 44-47), said modified proteins have been modified by conjugation to a transport aid that facilitates the cellular uptake of said therapeutic protein (col. 4, lines 44-47).

Neither Elsberry nor Allen teaches the conjugation comprises a linker species existing between said therapeutic protein and said transport aid; said linker is a streptavidin-biotin complex.

Beliveau teaches the conjugation comprises a linker species existing between said therapeutic protein and said transport aid (para. 26); said linker is a streptavidin-biotin complex (para. 189).

Neither Elsberry, Allen or Beliveau teaches linking the protein with the transport aid in a pH-dependent manner wherein the therapeutic protein and transport aid remain operably linked in a neutral pH environment, and the therapeutic protein disassociates at an acidic pH.

Axworthy teaches linking the protein with the transport aid in a pH-dependent manner (col. 19, lines 29-40).

But Elsberry, Allen, Beliveau, or Axworthy teaches that the therapeutic protein and transport aid remain operably linked in a neutral pH environment, and the therapeutic protein disassociates at an acidic pH.

Athappilly teaches the therapeutic protein and transport aid remain operably linked in a neutral pH environment, and the therapeutic protein disassociates at an acidic pH (abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have included the therapeutic protein formulation of Allen, and the linker species of Beliveau in the system of Elsberry, in order to in order to reduce therapeutic protein loss to clearance and inactivation (col. 1, lines 48-51, 62-64) as taught by Allen, and to modulate blood-brain barrier transport (abstract) as taught by Beliveau.

Furthermore, one of ordinary skill would have found it obvious to include a pH dependent linkage of Axworthy and the low pH dissociation of Athappilly in the system of Elsberry, Allen, and Beliveau, in order to provide clearing agents to facilitate removal of circulating targeting complexes (col. 1, lines 58-64) as taught by Axworthy.

In regards to claims 2-6, 9, 10, 12, 14, 18-21, 23-26, 29-33, 45-49, 51-52, 55-59, 62, 63, 65, 66, 69-75, 129-140, Elsberry, as modified by Allen and Beliveau, teaches the system of claims 1, 28, and 54, and further teaches:

Claims 2, 29, 55: the neurological diseases treated are selected from the group consisting of lysosomal storage diseases, protein deficiency diseases, enzyme deficiency diseases, inborn errors of metabolism, neurodegenerative diseases (col. 2, lines 19-21), and combinations thereof;

Claims 3, 30, 56: said neurological diseases are inborn errors of metabolism selected from the group consisting of … mucopolysaccharidosis (Allen Table 1, line 32);

Claims 4, 31, 57: said neurological diseases are selected from the group consisting of Fragile X Syndrome, Parkinson's disease (Elsberry col. 2, line 20), Alzheimer's disease, and combinations thereof;

Claims 5, 32, 58: the therapeutic protein formulation comprises enzymes providing for enzyme replacement therapy (Allen col. 1, lines 38-42);

Claims 6, 33, 59: the enzymes are selected from the group consisting of … alpha-L-iduronidase (Allen Table 1, line 32);

Claims 9, 62: said modified proteins have been modified by incorporating into their structure amino acid sequences providing for an intrinsic transport aid (col. 4, lines 44-47);

Claims 10, 63: said modified proteins are fusion proteins (col. 4, lines 44-47 – by conjugating one is also fusing two proteins together into one peptide);

Claims 12, 65: the transport aid comprises at least a portion of a species selected from the group consisting of recombinant human melanotransferrin, p97, tetanus toxin fragment C, endogenous lectins (Allen col. 4, lines 61-64), biotin, and combinations thereof;

Claims 14, 66: said linker is selected from the group consisting of peptide linkages, disulfide linkages, and combinations thereof (Beliveau para. 26);

Claims 18, 45, 69: implantable catheter system is implanted so as to deliver said therapeutic protein formulation to regions selected from the group consisting of... intracerebroventricular (Elsberry col. 2, lines 29-32);

Claims 19, 70: further comprising an inlet (Fig. 12, #14);

Claims 20, 48, 71: further comprising a reservoir (Elsberry col. 3, lines 17-20);

Claims 21, 49, 72: said reservoir is implantable and refillable (col. 3, lines 15-20);

Claims 23, 51, 73: the pump comprises an integrated reservoir (col. 3, lines 15-20 – implies an integrated reservoir for the inlet 14 to connect to something);

Claims 24, 52, 74: said pump is implantable (Elsberry col. 2, lines 19-22);

Claims 25, 46, 75: the implantable catheter system comprises at least one branched catheter permitting delivery to at least two separate regions using one primary catheter line (Elsberry col. 3, lines 47-51);

Claims 26, 47: the branched catheter is bifurcated (col. 3, line 47 – "divided into twin tubes" implies a bifurcation);

Claims 129, 131, 133: the streptavidin-biotin complex is an engineered variant of an avidin or streptavidin and biotin pair (Athappilly abstract, pg. 1338, col. 1, lines 10-15), wherein the therapeutic protein is linked to either the avidin or the biotin, and the transport aid is linked to the other of the avidin or biotin (Axworthy col. 2, lines 1-7 – shows by example that a radionuclide can be attached to streptavidin with a targeting moiety, or the targeting moiety attached to biotin administered before streptatividin

radionuclide, or biotin radionuclide bound to previously administered streptavidin targeting moiety, one of ordinary skill would understand that the binding sites were interchangable and radionuclide and targeting moieties could be substituted for therapeutic protein and transport aid. See MPEP 2144.04);

Claims 130, 132, 134: the linker is a streptavidin and 2'-iminibiotin complex (Athappilly abstract) linking the therapeutic protein (Allen col. 4, lines 44-47) with the transport aid in a pH-dependent manner (Athappilly abstract), wherein the therapeutic protein and transport aid are operably linked in a neutral pH environment of the cerebral spinal fluid of the patient, and disassociate in lysosomal departments or other acidic intracellular organelles of the patient (Athappilly abstract, pg. 1338, cols. 1-2 – one of ordinary skill would understand that dissociation of the therapeutic protein and transport aid would occur at low pH values wherever in the body those might be located).

Claims 135-137: delivery of said therapeutic protein formulation across the blood-brain barrier of patients comprises delivery to the central nervous system (Elsberry Fig. 1, #22A – shows catheters into the brain which is part of the central nervous system), and wherein the system provides for enhanced transcytosis of therapeutic proteins into cells (see rejection of claims 1, 28, and 54 above);

Claim 138-140: delivery of said protein formulation is in vivo (Elsberry Fig. 1, #22A – shows catheters into the brain which is in vivo delivery).

4. Claims 7, 16, 17, 34, 44, 60, and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elsberry, as modified by Allen and Beliveau, as applied to claims 1, 28, and 54 above, and further in view of U.S. Patent 6,015,572 to Leu-Fen H. Lin et al. (Lin).

In regards to claims 7, 34, and 60, Elsberry, as modified by Allen and Beliveau, teaches the system of claims 1, 28, and 54, but does not teach the therapeutic protein formulation comprises proteins selected from the group consisting of GDNF, FMRP, and combinations thereof.

Lin teaches the therapeutic protein formulation comprises proteins selected from the group consisting of GDNF (col. 1, lines 25-27), FMRP, and combinations thereof.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have included the GDNF proteins of Lin in the system of Elsberry, as modified by Allen, in order to treat nerve damage and related diseases (col. 1, lines 25-27) as taught by Lin.

In regards to claims 16, 17, 44, and 68, Elsberry, as modified by Allen and Beliveau, teaches the system of claims 1, 28, and 54, but does not teach said therapeutic protein formulation has been formulated to help maintain the integrity and activity of the protein formulation; the integrity and activity of the protein formulation is achieved by the addition to said therapeutic protein formulation, at least one species operable for maintaining a desired pH.

Lin teaches said therapeutic protein formulation has been formulated to help maintain the integrity and activity of the protein formulation; the integrity and activity of the protein

formulation is achieved by the addition to said therapeutic protein formulation, at least one species operable for maintaining a desired pH (col. 19, lines 50-64).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have further included the pH maintaining excipients of Lin in the system of Elsberry, as modified by Allen, in order to provide a "physiologically-compatible, slow-release formulation" (col. 19, lines 50-52) as taught by Lin.

Response to Amendment

5. The addition of new claims 135-140 in the response filed on 13 December 2010 is acknowledged.

Response to Arguments

6. Applicant's arguments filed 12 December 2010 have been fully considered but they are not persuasive.

7. Applicant argues that Athappilly et al. teaches away from a streptaviding-biotin complex and fails to contemplate therapeutic use (Remarks pgs. 15-16), however this is not persuasive because Athappilly discusses a biotin analogue, namely 2'-iminobiotin whose affinity for strepavidin decreases as pH decreases (abstract), the binding strength decreases as the pH decreases (pg. 1338, col. 1, lines 2-4, "In contrast...pH decreases"), and "if streptavidin were to bind the protontaed 2'-iminobiotin, this binding would be expected to be very weak" (pg. 1341, col. 1, lines 4-5), which indicate that a streptavidin-biotin analogue does contain the necessary pH-dependent binding characteristics recited in claims 1, 28, and 54. Athappilly, does not disclose a therapeutic use because Athappilly is directed to the chemical structure of 2'-iminobiotin that provides its pH-dependent streptavidin binding functionality, or more

specifically the low pH dissociation of streptavidin-2'-iminobiotin, where Allen teaches modification of proteins by conjugation to a transport aid for enhanced cellular uptake, while Beliveau specifically teaches a streptavidin-biotin linker complex, and Axworthy teaches a pH-depending binding via streptavidin-biotin (see rejection above).

8. Applicant argues that "Athappilly et al. teaches the opposite conclusion with respect to the streptavidin-biotin complex of claim 1" and then argues that this teaching does not conflict with the streptavidin-biotin complex of claim 1, because one of ordinary skill would not understand from Athappilly that dissociation of the therapeutic protein and transport aid would occur at low pH values where ever in the body those might occur, since Athappilly is directed to affinity chromatography and not in vivo treatment of a human patient (Remarks pg. 16). This is not persuasive because, as stated in the Non-Final Rejection mailed on 12 August 2010, Athappilly is not directed to a function of streptavidin-biotin that is only present in affinity chromatography it is directed to an inherent feature of the chemical structure of streptavidin-biotin, and 2'-iminobiotin analogue. Indeed, Athappilly states as much, "in order to understand the molecular details of this pH-dependent binding, we analyzed the crystal structures of the complex of core streptavidin with 2'-iminiobiotin at pH values 4.0 and 7.5" (abstract, lines 5-7). Athappilly only states that "this [pH-dependent binding] property is useful in the isolation of streptavidin and iminobiotinylated molecules by affinity chromatography" (pg. 1338, col. 1, lines 5-7) which is an intended use of the unique molecular structure of the streptavidin-2'-iminobiotin complex.

9. Additionally, if applicant argues that streptavidin-biotin complex does not have pH-dependent binding based on the teachings of Athappilly, which as described above is directed to

the molecular structure of streptavidin-2'-iminobiotin an analogue of the streptavidin-biotin complex, then applicant's streptavidin-biotin complex of claims 1, 28, and 54 would also be incapable of this pH-dependent binding.

10. Applicant argues that the application of pH-dependent binding to in vivo drug delivery across the blood-brain barrier unexpected, regarding the differences in design and purpose of crystallographic analysis or affinity chromatography (Remarks pg. 16-17). However as stated above, this is not an unexpected use of a linker complex such as streptavidin-biotin and 2'-iminobiotin analogue, because Athappily is not directed to the application in affinity chromatography, but rather to understanding the molecular structure that provides the pH-dependent binding functionality (see response to arguments above para. 8).

11. In response to applicant's argument that Athappilly does not teach the use of the complex in cerebral spinal fluid or in lysosomal department of the patient (Remarks pg. 17), a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

12. Applicant argues that Beliveau teaches that the linker is a non-critical aspect of the invention (Remarks pg. 17-18), however this is not persuasive because, as stated in the Office Action mailed 12 August 2010, para. 187 states that "the particular lab or detectable group used is not a critical aspect of the invention..." and goes on to say in para. 189 "generally, a ligand molecular (e.g. biotin) is covalently bound to the molecule. The ligand then binds to another molecules (e.g streptavidin) molecule, which is either inherently detectable or covalently bound

to a signal system, such as a detectable enzyme, a fluorescent compound, or a chemiluminescent compound" which shows that its the detectable compound that is non-critical not the linker between the detectable compound and the protein.

13. Applicant argues that Axworthy and Athappilly does not show that a streptavidin-biotin linker is well known, specifically the pH-dependent binding of Athappilly was known as well as the streptavidin-biotin conjugation to proteins of Axworthy. Furthermore, linking between two proteins is taught by Axworthy as an antibody and cytokine are proteins used in the immune system.

14. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the specification teaches that acceptable levels of solution pH for the therapeutic protein formulation of the invention are those that "generally maintain the integrity of the therapeutic protein/enzyme" (Remarks pg. 19)) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Conclusion

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LARRY R. WILSON whose telephone number is (571)270-5899. The examiner can normally be reached on Monday-Thursday 7:00 AM - 5:30 PM (EST).

17. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kevin C. Sirmons can be reached on 571-272-4965. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

18. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LARRY R WILSON/
Examiner, Art Unit 3767
/KEVIN C. SIRMONS/
Supervisory Patent Examiner, Art Unit 3767